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Effects of dexamethasone on declarative memory function in posttraumatic stress disorder

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Abstract

Alterations in the hypothalamic–pituitary–adrenal (HPA) axis and hippocampal-based memory have been associated with posttraumatic stress disorder (PTSD), and the administration of exogenous glucocorticoids has been shown to result in a transient verbal declarative memory impairment in healthy human subjects. The purpose of this study was to assess the effects of the glucocorticoid dexamethasone on verbal declarative memory function in patients with PTSD. Forty-two men and women with (n=14) and without (n=28) PTSD received placebo or dexamethasone (1 and 2 mg on two successive days) in a double-blind, randomized fashion. Declarative memory was assessed with paragraph recall at baseline (day 1) and day 3. There was a significant interaction between diagnosis and drug (dexamethasone vs. placebo) on paragraph recall related to a relative detrimental effect of dexamethasone on memory function in healthy subjects, but not those with PTSD. These findings are consistent with an altered sensitivity of declarative memory function in PTSD to regulation by glucocorticoids, possibly explainable by alterations in glucocorticoid receptors in the hippocampus or other brain regions mediating declarative memory.

Keywords: PTSD; Memory; Dexamethasone; Cortisol; Glucocorticoids; Hippocampus

1. Introduction

Alterations in cognition and memory are an important aspect of the clinical presentation of posttraumatic stress disorder (PTSD). Empirical stud-

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ies have shown problems with learning and memory in PTSD that are specific to verbal declarative memory functions, such as the learning of new words or paragraphs (Gil et al., 1990; Bremner et al., 1993; Uddo et al., 1993; Bremner et al., 1995a; Yehuda et al., 1995b; Barrett et al., 1996; Golier et al., 1997; Jenkins et al., 1998; Vasterling et al., 1998; Moradi et al., 1999; Sachinvala et al., 2000; Gilbertson et al., 2001; Roca and Freeman, 2001; Vasterling et al., 2002). Understanding the neurobiological basis of memory alterations in PTSD may promote the development of new treatment approaches for this disabling aspect of PTSD.

The hypothalamic–pituitary–adrenal (HPA) axis plays a critical role in the stress response as well as modulating memory function (Heffelfinger and Newcomer, 2001). Patients with PTSD were found to have increased levels of corticotropin releasing factor (CRF) (Bremner et al., 1997a; Baker et al., 1999), enhanced cortisol suppression with dexamethasone (Yehuda et al., 1993), increased lympocyte glucocorticoid receptors (Yehuda et al., 1991a), lower resting cortisol levels in some studies (Yehuda et al., 1991b; Yehuda et al., 1994; Yehuda et al., 1995a; Kanter et al., 2001) but not others (Pitman and Orr, 1990; Lemieux and Coe, 1995) and increased cortisol response to stressors (Heim et al., 2000; Elzinga et al., 2003; Bremner et al., 2003a). The hippocampus is involved in memory (Zola-Morgan and Squire, 1990) as well as regulation of the HPA axis. (Herman et al., 1989). Stress results in alterations in hippocampal structure, an effect hypothesized to be secondary, at least in part, to stress-induced release of glucocorticoids (Pavlides et al., 1995; Diamond et al., 1996; Sapolsky, 1996) with associated inhibition of new neuronal growth (Gould et al., 1998; Malberg et al., 2000) and deficits in memory (Arbel et al., 1994; Luine et al., 1994). Mechanisms that have been proposed for the negative effects of stress on the hippocampus include increased activation of the type 2 glucocorticoid receptors (Sapolsky et al., 1990; Newcomer et al., 1994; Sapolsky, 1996), stress-induced decreases in brain-derived neurotrophic factor (BDNF) (Nibuya et al., 1995; Smith et al., 1995; Malberg et al., 2000; Duman et al., 2001), increased levels of excitatory amino acids (Moghaddam et al., 1997) and alterations in serotonin (McEwen et al., 1997).

Elevations of glucocorticoids within the physiological range result in reversible deficits in memory function in animals (Oitzl and de Kloet, 1992; Bodnoff et al., 1995) as well as human subjects (Newcomer et al., 1994; Kirschbaum et al., 1996; Lupien et al., 1997; Lupien et al., 1999; Newcomer et al., 1999; de Quervain et al., 2000; Wolf et al., 2001; Lupien et al., 2002). Glucocorticoids released during stress, possibly acting through the hippocampus, may explain in part the acutely reversible as well as chronic effects that stress has on declarative memory (Kirschbaum et al., 1996; Porter and Landfield, 1998; de Kloet et al., 1999; Wolf, 2003). Greater deficits are seen in younger subjects in comparison to older subjects, hypothesized to be secondary to age-related decreases in glucocorticoid receptor density (Newcomer et al., 1995). Studies in other neuropsychiatric disorders associated with hippocampal dysfunction, including schizophrenia (Newcomer et al., 1998) and depression (Bremner et al., 2004), found a relative sparing of the effects of dexamethasone on declarative memory function relative to normal human subjects, hypothesized to be secondary to disease-related decreases in glucocorticoid receptor function. PTSD has been described as an "accelerated aging" (Bremner and Narayan, 1998) related to common theories of progressive hippocampal atrophy and dysfunction in both processes. Therefore, it might be expected that dexamethasone would have less of an effect on verbal declarative memory function in PTSD than in controls. The purpose of the present study was to assess the effects of dexamethasone on verbal declarative memory function in patients with PTSD. We hypothesized that glucocorticoids would have less of an effect on declarative memory function in PTSD than in controls.

2. Methods

2.1. Subjects

Forty-two male and female subjects who were 18 years of age or older participated in the study. Subjects were included with (n=14) and without PTSD (n=28). All subjects were recruited by advertisement and gave written informed consent for participation in the study. This study was approved by the Yale University Investigational Review Board. PTSD subjects were included with the diagnosis of

PTSD based on the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995). PTSD patients had experienced a range of traumas including childhood abuse, motor vehicle accident, rape, assault, and combat. Subjects were excluded if they presented with a history of current alcohol or substance abuse or dependence in the past 6 months, schizophrenia, or an eating disorder as determined by the SCID, serious medical disorder as determined by laboratory tests and physical examination, organic mental disorder, neurological disorder, or head trauma. All subjects were medication free 4 weeks or more before the study.

Non-PTSD subjects met the same inclusion criteria for PTSD subjects with the exception of having a diagnosis of PTSD based on the SCID. Non-PTSD subjects did not have a history of major traumas as measured by the Early Trauma Inventory (ETI) and did not have a history of psychiatric disorder as measured by the SCID. There was no difference in age between the groups (Table 1).

2.2. Assessments

All subjects were evaluated with the SCID for comorbid psychiatric diagnoses. Eight out of 14 PTSD subjects (57%) fulfilled criteria for a lifetime history of major depression and four (29%) for current major depression. One subject (7%) fulfilled criteria for lifetime and current history of panic disorder without agoraphobia, two subjects (14%) fulfilled criteria for lifetime and current history of panic disorder with agoraphobia, one subject (7%) had a current and lifetime history of generalized anxiety disorder, two (14%) current and lifetime simple phobia, and one (7%) current and lifetime social phobia. Two (14%) subjects met criteria for lifetime (not current) bulimia. None of the subjects had current (past 6 months) alcohol or substance abuse/dependence. Two PTSD subjects (14%) fulfilled criteria for a lifetime history of alcohol dependence, one (7%) for lifetime history of alcohol abuse, one (7%) for lifetime history of polysubstance dependence, one (7%) for marijuana dependence, one (7%) for marijuana abuse, one (7%) for cocaine abuse, one (7%) for cocaine dependence, and one (7%) for polysubstance dependence.

All PTSD subjects were assessed with the Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995), a reliable and valid measure of PTSD symptom level with subcomponents for the individual symptom clusters. Subjects were also assessed with the Civilian Version of the Mississippi Scale for Combat-Related PTSD, a self-report measure of current PTSD symptom severity that is a continuous measure (Vreven et al., 1995). Severity of childhood abuse was evaluated with the Early Trauma Inventory (ETI), a reliable and valid instrument for assessment of childhood and adult abuse and trauma (Bremner et al., 2000). The ETI has components for measurement of general childhood trauma (e.g., being in an accident or a natural disaster), physical, emotional, and sexual abuse. The ETI contains indexes for measurement of severity of trauma in each of the subcomponents based on number of endorsed items, duration, and frequency. The ETI

Table 1
Demographic and psychometric data in PTSD and non-PTSD subjects[a]

	PTSD Dex (n=7)	PTSD Placebo (n=7)	Non-PTSD Dex (n=13)	Non-PTSD Placebo (n=15)	F value[b]	P value
Age	42 (8)	42 (10)	41 (11)	43 (10)	3.11	0.09
Sex	7 F	7 F	8F/5M	11F/4M		
Years of education	15 (3)	16 (2)	16 (2)	17 (2)	2.82	0.10
ETI Trauma Severity Index (Total)	74 (24)	91 (26)	14 (15)	12 (17)	98.21	<0.0001
CAPS (PTSD symptoms) score	84 (22)	72 (22)				
CADSS (dissociation) score	15 (18)	4 (5)	0.7 (2.0)	1.1 (2.1)	8.13	0.008[c]

Numbers in parentheses are standard deviation (S.D.).

[a] There were 14 PTSD subjects, of whom 7 were randomized to dexamethasone (PTSD Dex) and 7 to placebo (PTSD Placebo); there were 28 non-PTSD subjects, of whom 13 were randomized to dexamethasone (Non-PTSD Dex) and 15 to placebo (Non-PTSD Placebo).

[b] Main effect for diagnosis; age and education, df=1,38; ETI, df=1,30, CADSS, df=1,28.

[c] Post hoc test showed no difference between PTSD Dex and PTSD Placebo in CADSS score.

Trauma Severity Index is the sum of scores for severity indexes in the subcomponents. The scoring and psychometric properties of the ETI and ETI-based indexes are described in detail elsewhere (Bremner et al., 2000). Baseline dissociative state symptom levels were assessed with the Clinician Administered Dissociative States Scale (CADSS), a reliable and valid instrument (Bremner et al., 1998). Current depressive symptoms were assessed with the Hamilton Depression Scale (Ham-D; Hamilton, 1960). State anxiety was measured with the Hamilton Anxiety Scale (Ham-A; Hamilton, 1959). Depression and anxiety were assessed at the same time as the neuropsychological testing of memory (i.e. at 16.00 h on day 1 and 16.00 h on day 2). Table 1 presents psychometric data collected with these instruments.

2.3. Assessment of memory after administration of dexamethasone and placebo

Subjects were administered dexamethasone or placebo in a double-blind randomized design. Specifically, subjects were administered 1 mg dexamethasone or placebo by mouth at 23.00 h on day 1 and 2 mg dexamethasone or placebo by mouth at 23.00 h on day 2. Neuropsychological testing of memory, as well as behavioral ratings of mood and anxiety, were performed at 16.00 h on days 1 and 3. Serial memory function (paragraph recall) was assessed as previously described (Newcomer et al., 1994, 1998). Subjects were read two paragraphs on day 1 with assessment of recall both immediately and after a 30-min delay, and two different paragraphs with immediate and delayed recall on day 3, in order to assess glucocorticoid effects on declarative memory. The number of correctly recalled elements of the paragraph was scored, and scores on the two paragraphs were summed for immediate and delayed recall. Percent retention was calculated by dividing delayed recall by immediate recall. In situations where more elements were recalled with delayed than immediate recall, the percent retention score was greater than 100%. Percent retention of the paragraph was the primary outcome of this study and is a reflection of memory consolidation. The rationale for using this measure is that deficits have previously been correlated with integrity of hippocampal neurons (Sass et al., 1990, 1995) and we have shown deficits on this measure in our prior studies of PTSD (Bremner et al., 1993, 1995a). Deficits percent retention are felt to reflect hippocampal dysfunction; however, other brain areas such as the prefrontal cortex may be involved in a circuit mediating this cognitive function.

2.4. Data analysis

Repeated measures analysis of variance (ANOVA) with treatment (dexamethasone vs. placebo) and diagnosis group (PTSD vs. controls) as factors, and time as the repeated factor, was used to assess the effects of dexamethasone on memory function over time in the two groups. For analyses assessing the relationship of behavioral and memory variables, the delta of percent retention of paragraph was calculated for baseline and post treatment. Pearson correlations were used to assess the relationship between behavioral variables and the effects of dexamethasone on memory function. Significance was defined as $P<0.05$.

3. Results

3.1. Effects of dexamethasone on declarative memory function

Dexamethasone resulted in a differential effect on declarative memory function in PTSD and non-PTSD subjects. In the non-PTSD subjects, there was a pattern of a relative decrement in verbal declarative memory function consistent with prior reports (Newcomer et al., 1994, 1999). In the PTSD patients, this pattern was not observed, leading to an interaction between diagnosis and the effect of dexamethasone on declarative memory function (Fig. 1; Table 2).

3.2. Relationship between behavioral factors and the effects of dexamethasone on declarative memory function

Dexamethasone administration did not result in a reduction in depression or anxiety as measured by the Ham-D or Ham-A, respectively. There were no

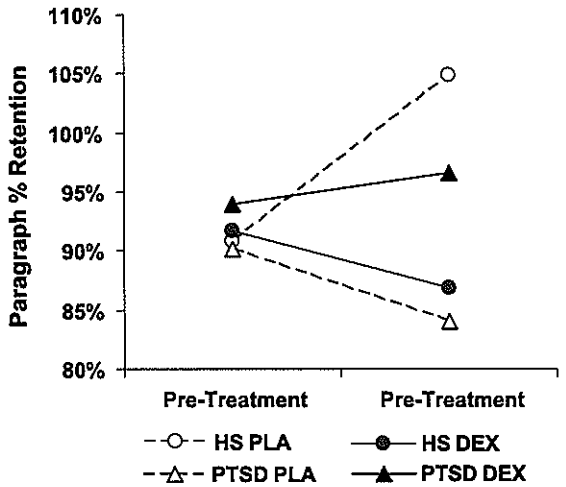

Fig. 1. Effects of dexamethasone and placebo on paragraph recall (percent retention) in PTSD and non-PTSD subjects. There was a significant interaction between diagnosis (PTSD vs. non-PTSD) treatment (pre-treatment vs. post-treatment) and drug (dexamethasone vs. placebo) on memory function, related to a pattern of a relative sparing of the negative effects of dexamethasone on memory function in PTSD versus non-PTSD subjects (F=2.86; df=3,81; P<0.05).

differences in the effect of dexamethasone on depression or anxiety between patients with PTSD or controls. There was no significant relationship between baseline PTSD symptom severity as measured by the CAPS, dissociation as measured by the CADSS, depression as measured by the Ham-D before or after treatment, anxiety as measured by the Ham-A before or after treatment, or abuse severity as measured by the ETI, and change in declarative memory function with dexamethasone in the PTSD subjects. There were no differences between healthy men and women in the effects of dexamethasone on declarative memory function.

4. Discussion

Dexamethasone had a differential effect on verbal declarative memory function in PTSD subjects in comparison to healthy control subjects, with a relative impairment in retention and/or retrieval observed in healthy controls, but not in subjects with PTSD.

There are several possible explanations for these findings. As noted above, studies in animals showed that cortisol interferes with memory consolidation (Oitzl and de Kloet, 1992; Bodnoff et al., 1995; McGaugh, 2000). Studies have also shown a relationship between elevations of glucocorticoids and deficits in declarative memory function (Newcomer et al., 1994; Kirschbaum et al., 1996; Lupien et al., 1997, 1998). Glucocorticoids may interfere with the consolidation and/or retrieval of memory in human subjects (Newcomer et al., 1994; Kirschbaum et al., 1996; Lupien et al., 1997, 1999; Newcomer et al., 1999; de Quervain et al., 2000; Wolf et al., 2001; Lupien et al., 2002). Newcomer et al. (1994) administered dexamethasone for 4 consecutive days (0.5, 1, 1, 1 mg, respectively) with a resultant progressive impairment in short-term verbal memory performance. In another similarly designed study, deficits in short-term memory were seen to a greater degree in younger subjects than in older subjects (Newcomer et al., 1995). Extrapolating from this latter study to PTSD, one hypothesis is that the down-regulation of glucocorticoid receptors, with or without loss of hippocampal neurons, which can occur during normal aging (Bhatnagar et al., 1997), may also occur in PTSD. In this scenario, the smaller effect of dexamethasone on memory function is due to a loss of glucocorticoid receptor function in both normal aging and in PTSD.

Table 2
Memory and mood scores with placebo and dexamethasone in PTSD and non-PTSD subjects

	PTSD Dex Pre	PTSD Dex Post	PTSD Placebo Pre	PTSD Placebo Post	Non-PTSD Dex Pre	Non-PTSD Dex Post	Non-PTSD Placebo Pre	Non-PTSD Placebo Post	F value**	P value
Par-I	55 (11)	49 (12)	51 (7)	46 (8)	50 (13)	50 (12)	60 (14)	52 (14)	1.20	0.29
Par-D	52 (12)	47 (10)	46 (8)	39 (9)	46 (13)	44 (14)	54 (13)	54 (16)	0.27	0.61
Par-R	93% (9)	94% (8)	90% (6)	83% (11)	92% (14)	87% (16)	91% (6)	105% (23)	4.52	0.04
Ham-D	32.3 (17.5)	25.4 (19.2)	23.4 (16.3)	16.3 (10.9)	2.5 (5.7)	1.5 (2.1)	3.4 (6.4)	2.7 (4.7)	0	0.99
Ham-A	13.7 (8.7)	10.9 (10.5)	14.7 (5.4)	11.3 (7.7)	1.5 (2.6)	1.8 (3.5)	1.5 (3.7)	1.7 (2.2)	0.44	0.51

* Diagnosis by drug interaction; paragraph, df=1,38, Ham-D, df=1,33, Ham-A, df=1,31.

Animal models of stress also support a decrease in glucocorticoid receptor sensitivity in the hippocampus. Maternally deprived rats had decreased numbers of glucocorticoid receptors in the hippocampus (Ladd et al., 1996). Other studies showed that stressed animals demonstrated an inability to terminate the glucocorticoid response to stress (Sapolsky et al., 1984a,b) which could be related to decreased glucocorticoid receptor binding in the hippocampus (Makino et al., 1995). Complicating this model, however, are studies showing increased glucocorticoid receptors measured on lymphocytes in PTSD (Yehuda et al., 1991a) and increased negative feedback of cortisol suppression with dexamethasone in PTSD (Yehuda et al., 1993), which suggests that dexamethasone would have a greater effect on memory function in PTSD (Yehuda et al., 1991a). However, these studies do not provide information about glucocorticoid receptors in the hippocampus. In addition, metyrapone studies have had mixed results, with some studies showing increased ACTH and 11-deoxycortisol levels following cortisol synthesis inhibition with metyrapone (Yehuda et al., 1996), consistent with increased negative feedback, while other studies found no increases in ACTH with metyrapone (Kanter et al., 2001). Further complicating this issue are questions about whether the human hippocampus has a high concentration of type II glucocorticoid receptors (Sanchez et al., 2000) and the degree to which dexamethasone crosses the blood–brain barrier (Stumpf et al., 1989; Birmingham et al., 1993). If dexamethasone does not readily cross the blood–brain barrier, this raises the question of whether dexamethasone exerts an effect directly, or whether suppression of the HPA axis is accountable for findings of memory deficits. Consistent with the latter explanation are studies in animals showing memory consolidation deficits with removal of glucocorticoids through adrenalectomy (Oitzl and de Kloet, 1992). PTSD patients, however, were found to have increased suppression of cortisol with dexamethasone (Yehuda et al., 1993). If low levels of cortisol accounted for the finding of memory impairment after dexamethasone, a relatively greater effect of dexamethasone in PTSD would be expected, the opposite of what was found in the current study.

These findings are consistent with the hypothesis of hippocampal dysfunction in PTSD. Studies in animals showed that stress results in damage to the hippocampus (which plays a role in learning and memory) (McEwen et al., 1992; Sapolsky, 1996) with associated inhibition of new neuronal growth (Gould et al., 1998; Malberg et al., 2000) and deficits in memory (Arbel et al., 1994; Luine et al., 1994). Studies in humans showed that deficits in retention of a paragraph over time (measured with the Wechsler Memory Scale; Logical Memory-Percent Retention) were correlated with a loss of neurons in the hippocampus (Sass et al., 1990). Subsequent studies have demonstrated verbal declarative memory deficits in PTSD (Golier and Yehuda, 1998; Buckley et al., 2000; Brewin, 2001; Elzinga and Bremner, 2002). As reviewed above, several studies found specific deficits in verbal declarative memory function, with a relative sparing of attention, visual memory, and IQ (Gil et al., 1990; Bremner et al., 1993, 1995a; Uddo et al., 1993; Yehuda et al., 1995b; Barrett et al., 1996; Golier et al., 1997; Jenkins et al., 1998; Vasterling et al., 1998; Moradi et al., 1999; Sachinvala et al., 2000; Gilbertson et al., 2001; Roca and Freeman, 2001; Vasterling et al., 2002). Similarly, smaller hippocampal volume measured with magnetic resonance imaging (MRI) has been found in patients with PTSD (Bremner et al., 1995b, 1997b, 2003b; Gurvits et al., 1996; Stein et al., 1997; Gilbertson et al., 2002; Villareale et al., 2002). All of these studies, together with the current study, are consistent with hippocampal dysfunction, altered cortisol responsiveness, and altered sensitivity to declarative memory function in PTSD.

There were several limitations of the current study. Subjects were not matched for sex, and there were more females in the PTSD group. However, we did not find any differences in the effects of dexamethasone on memory function by sex. Data on smoking history, which may affect HPA function, were not collected. There were no differences in immediate and delayed recall when examined separately, unlike findings in prior studies. The outcome measure of percent retention can be influenced by changes in both immediate and delayed recall. PTSD patients did not show deficits in recall at baseline compared with controls, unlike our prior studies (Newcomer et al., 1994). This was a small study

sample, however, and the memory testing material was not the same as that used in prior published studies. Healthy subjects showed better memory after placebo than at baseline, an effect not seen in PTSD patients. This is likely attributable to a practice effect that was blocked by dexamethasone. An absence of a practice effect in the PTSD patients is consistent with cognitive deficits in PTSD. Several of the PTSD patients had a history of depression. Since we have previously reported similar findings in patients with primary depression, we cannot exclude depression as contributing to the findings (Bremner et al., 2004). We did not include a control group of traumatized non-PTSD subjects and therefore cannot determine whether the effects are specific to PTSD or are a nonspecific effect of trauma exposure. Future studies should look at subjects with a history of trauma exposure without PTSD.

Findings of the current study may have implications for the treatment of PTSD. Increasingly, symptoms seen in PTSD that are not included among the traditional DSM criteria, like cognitive disturbances, are becoming recognized as making an important contribution to the disability of patients with PTSD. Medications that have actions on glucocorticoid receptors in the hippocampus may lead to improvements in both cognition and possibly PTSD symptoms. Understanding the interaction between HPA axis function, hippocampal function, and declarative memory may also point to new treatment approaches for PTSD.

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